uct, taken in chloroform solution at 60° and 60 M c.p.s. with a tetramethylsilane internal reference standard, included a singlet at $\tau$ 7.76 attributable to the terminal deoxy group. The n.m.r. spectra of other terminal deoxy sugars have been shown[36] to possess similar high field signals.

(36) M. L. Wolfrom, K. Matsuda, F. Komitsky, Jr., and T. E. Whiteley, *J. Org. Chem.*, **28**, 3551 (1963).

*Anal.* Calcd. for $C_{26}H_{22}O_7$: C, 69.95; H, 4.97; sapon. value, 6.72 ml. of 0.01 *N* NaOH/10 mg. Found: C, 69.79; H, 5.15; sapon. value, 6.81 ml. of 0.01 *N* NaOH/10 mg.

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# The Anomeric Pair of Phenyl Sedoheptulosides (Phenyl α- and β-D-*altro*-Heptulopyranosides) and Their Marked Lability toward Acid and Alkali

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The condensation of sedoheptulose hexaacetate and phenol, with zinc chloride as catalyst, has furnished us for the first time with an anomeric pair of phenyl heptuloside pentaacetates and, after deacetylation, the phenyl α- and β-sedoheptulosides (phenyl α- and β-D-*altro*-heptulopyranosides). These sedoheptulosides are hydrolyzed very readily by acids, even at room temperature. They are extremely sensitive toward alkalies: methanolic sodium methoxide converts then into methyl α-sedoheptuloside (which was synthesized independently for comparison) and dilute aqueous potassium hydroxide converts them very rapidly at room temperature into sedoheptulose and phenol. New data on the behavior of other phenyl heptulosides and hexosides toward alkali are reported; several new sedoheptulosan derivatives are described, together with n.m.r. data used in proving their structures; and some brief comments on the mechanism of the alkaline degradation of phenyl glycosides are added.

Earlier studies in this laboratory have been concerned with the biologically important sedoheptulose (D-*altro*-heptulose),[1] with the formation of nonreducing anhydro sugars by the action of acid on reducing sugars,[2] and with the degradation of phenyl glycosides to nonreducing anhydro sugars under the influence of alkalies.[3] This paper relates to all three of those topics.

Haskins, Hann, and Hudson[4] have described an isopropylidenesedoheptulosan. Through n.m.r. spectra we have established that the *O*-isopropylidene group is attached to C-4 and C-5, as expected; also that in the new monotosyl derivative of this compound the *O*-*p*-tolylsulfonyl group is attached at C-1, also as expected. The pertinent data are given in the Experimental section, together with descriptions of the ditosyl derivative of isopropylidenesedoheptulosan, of a high-melting modification of tetratosylsedoheptulosan, and of a crystalline sedoheptulosan 1,3,5-triacetate whose structure has been established through its n.m.r. spectrum.

Although the heptuloses and their derivatives, such as the penta- and hexaacetates, acetylated glycosyl halides, glycosides, etc., should be capable of existing in both α- and β-forms, no one to our knowledge has ever isolated previously anything but the α-anomer (α based on the optical rotation).[5] Although the *galacto*- and *talo*-heptuloses show mutarotation, it is not known what other species of sugar besides the α-anomer may exist in the equilibrium mixture.[6]

Starting with sedoheptulose hexaacetate,[1] phenol, and fused zinc chloride, by a modification of the Helferich and Schmitz-Hillebrecht synthesis,[7] we have succeeded in preparing phenyl α-sedoheptuloside pentaacetate in 84% yield and also, in very small yield, the phenyl β-sedoheptuloside pentaacetate, with rotations in chloroform of $[\alpha]^{20}D$ +60.7 and −94.6°, respectively. Careful deacetylation yielded the unique pair of crystalline phenyl α-sedoheptuloside (I) and phenyl β-sedoheptuloside with rotations in water of $[\alpha]^{20}D$ +121 and −145°, respectively. The pyranoside ring structures of these glycosides were established through the consumption of 2 moles of periodate and the liberation of 1 mole of acid/mole of compound.

The phenyl sedoheptulosides are extremely sensitive to acids and even a 5-min. contact at room temperature with the strongly acidic ion-exchange resin Amberlite IR-120($H^+$) was sufficient to afford a detectable amount of sedoheptulose while longer contact converted the liberated sugar into sedoheptulosan.

The phenyl sedoheptulosides are labile also toward alkalies. For example, the deacetylation of phenyl α-sedoheptuloside pentaacetate with methanolic sodium methoxide at 20° led to the isolation not only of phenyl α-sedoheptuloside but also of methyl α-sedoheptuloside. The latter was made independently through the Koenigs–Knorr synthesis and its pyranoside structure proved by oxidation with periodate. When the deacetylation was carried out at 65° the product appeared to be exclusively the methyl α-

(1) For the preceding paper on sedoheptulose, see N. K. Richtmyer and J. W. Pratt, *J. Am. Chem. Soc.*, **78**, 4717 (1956).

(2) For the preceding paper in this series, see L. C. Stewart, E. Zissis, and N. K. Richtmyer, *J. Org. Chem.*, **28**, 1842 (1963).

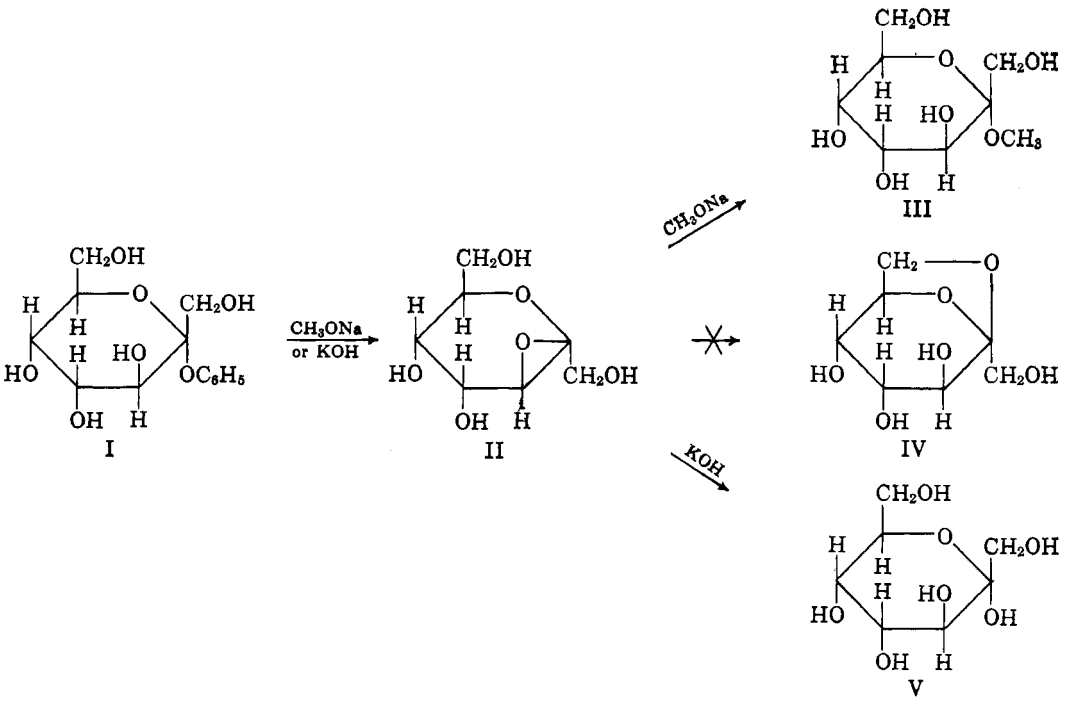
(3) For an earlier paper in this series, see E. Zissis and N. K. Richtmyer, *ibid.*, **26**, 5244 (1961).

(4) W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Am. Chem. Soc.*, **74**, 2198 (1952).

(5) This refers, of course, to the 2-heptuloses only, for R. Schaffer [*J. Org. Chem.*, **29**, 1473 (1964)] has described a levorotatory, mutarotating β-D-*manno*-3-heptulose.

(6) See R. S. Tipson and H. S. Isbell [*J. Res. Natl. Bur. Std.*, **66A**, 31 (1962)] for a study of the infrared absorption spectra of such equilibrium mixtures.

(7) B. Helferich and E. Schmitz-Hillebrecht, *Ber.*, **66**, 378 (1933); E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *J. Am. Chem. Soc.*, **64**, 690 (1942).




sedoheptuloside. By comparison, phenyl α-D-*gluco*-heptulopyranoside[8] and phenyl α-D-*manno*-heptulopyranoside[9] pentaacetates underwent simple deacetylation in methanolic sodium methoxide during 48 hr. at 20°, and the *gluco* compound was not further affected by boiling the solution for 48 hr. The phenyl α-D-*manno*-heptulopyranoside pentaacetate, however, was converted in a week in the boiling solution into about equal amounts of the phenyl and methyl α-D-*manno*-heptulopyranosides. The behavior of four phenyl hexosides toward hot methanolic sodium methoxide is described in the Experimental section.

The phenyl sedoheptulosides are extremely sensitive toward caustic alkali. Earlier, we had reported[8] that phenyl α-D-*gluco*-heptulopyranoside in boiling 1 *N* aqueous potassium hydroxide reached a constant rotation in 3 hr. and gave at least a 34% yield of 2,7-anhydro-β-D-*gluco*-heptulopyranose. Phenyl α-D-*manno*-heptulopyranoside similarly gave about an 8% yield of 2,7-anhydro-β-D-*manno*-heptulopyranose.[9] Considerable decomposition was evident in both cases. We now find that under the much milder conditions of 0.5 *N* aqueous potassium hydroxide at 20° the phenyl α-D-*gluco*-heptuloside remains unaffected after 4 days. Phenyl α-D-*manno*-heptuloside reacted slowly; paper chromatography showed that as the glycoside disappeared 2,7-anhydro-β-D-*manno*-heptulose was formed, and also D-*gluco*-heptulose but apparently no D-*manno*-heptulose. This reaction was confirmed by a similar experiment in which both the anhydro sugar and the D-*gluco*-heptulose were isolated in crystalline form. The presence of D-*gluco*-heptulose could be explained as follows: when D-*manno*-heptulose was allowed to stand in 0.5 *N* potassium hydroxide for 27 hr. paper chromatograms showed the epimeric heptuloses in equal amounts, but after 4 days only the D-*gluco*-heptulose remained; when D-*gluco*-heptulose was allowed to stand similarly, no evidence for its epimerization to D-*manno*-heptulose was observed.[10]

Phenyl α-sedoheptuloside, however, in 0.5 *N* potassium hydroxide at 20° reached a practically constant rotation in 3 hr. and paper chromatography indicated that the glycoside had been practically completely hydrolyzed to sedoheptulose and phenol at the end of that time. There was no evidence for the formation of sedoheptulosan or for the conversion of sedoheptulose into the epimeric D-*allo*-heptulose. The phenyl β-sedoheptuloside behaved similarly and the formation of sedoheptulosan from it was very doubtful. The continuing action of the alkali resulted in the complete destruction of all the heptuloses.

The qualitative behavior of the phenyl heptulosides toward hot Fehling solution was in accord with what could have been predicted from the results just described: the phenyl α-D-sedoheptuloside, phenyl α-D-*manno*-heptuloside, and phenyl α-D-*gluco*-heptuloside gave positive tests within 2, 20, and 30 min., respectively. Phenyl β-D-glucoside, phenyl β-D-galactoside, and phenyl α-D-galactoside (which had been reported[11] to be converted quantitatively by caustic alkali into the corresponding 1,6-anhydrides) gave negative tests after 3 hr. in a boiling water bath. Phenyl α-D-mannoside gave a positive test after 30 min. and a heavy red precipitate during 3 hr. in the boiling water bath; this was in agreement with the earlier report[11] that the product of the reaction of caustic alkali with phenyl α-D-mannoside was "mostly undetermined" and only about 5% of 1,6-anhydro-β-D-mannopyranose could be isolated as the isopropylidene derivative.

In a 1954 review on the alkali-sensitive glycosides, Ballou[12] has discussed three proposed mechanisms for the alkaline degradation of phenyl glycosides of aldoses. In the first and best established mechanism,

(8) L. C. Stewart, E. Zissis, and N. K. Richtmyer, *Chem. Ber.*, **89**, 535 (1956).

(9) E. Zissis, L. C. Stewart, and N. K. Richtmyer, *J. Am. Chem. Soc.*, **79**, 2593 (1957).

(10) E. M. Montgomery and C. S. Hudson [*ibid.*, **61**, 1654 (1939)] have isolated D-*gluco*-heptulose following the conversion of D-*glycero*-D-*galacto*-heptose into D-*manno*-heptulose by limewater.

(11) E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *ibid.*, **65**, 3 (1943).

(12) C. E. Ballou, *Advan. Carbohydrate Chem.*, **9**, 59 (1954).

the phenoxy group at C-1 (*e.g.*, in phenyl β-D-glucopyranoside) is eliminated together with the hydrogen atom from the *trans*-hydroxyl group at C-2 to form a 1,2-epoxide, which in turn is *trans* to the primary alcohol group at C-6. The backside attack of this hydroxyl group can then open the epoxide ring with the simultaneous formation of a 1,6-anhydro ring. Since the date of that review we have studied the alkaline degradation of phenyl α-D-*gluco*-heptulopyranoside[8] and phenyl α-D-*manno*-heptulopyranoside[9] and have suggested additional mechanisms that might account for the formation of the 34 and 8.4% yields of the respective 2,7-anhydrides that could be isolated from the reaction mixtures. In phenyl α-sedoheptuloside (I) the phenoxy group at C-2 is *trans* to the hydroxyl group at C-3 and elimination of phenol by sodium methoxide or by potassium hydroxide could result in the formation of a 2,3-epoxide (II, corresponding to a 1,2-epoxide in the aldose series). However, since this epoxide is *cis* to the primary alcohol group at C-7, no backside attack of that hydroxyl group on the epoxide is possible and the effect of the alkaline reagents would be to open the 2,3-epoxide ring with the formation of methyl α-sedoheptuloside (III) or sedoheptulose (V) but no sedoheptulosan (IV). So far, at least, this mechanism is not inconsistent with the first one proposed for certain examples in the phenyl hexoside series. The formation of 2,7-anhydrides from phenyl α-D-*manno*-heptulopyranoside (which would yield a 2,3-epoxide *cis* to the primary alcohol group at C-7) and from phenyl α-D-*gluco*-heptulopyranoside (which, like phenyl β-sedoheptuloside, has the phenoxy group at C-2 and the hydroxyl group at C-3 in a *cis* relationship and would not be expected to form a 2,3-epoxide) must depend upon other mechanisms. Perhaps additional studies with phenyl glycosides of other heptuloses, both substituted and unsubstituted, will lead to proposals of satisfactory mechanisms that will explain either the formation or nonformation, as the case may be, of 2,7-anhydrides by the alkaline degradation of phenyl heptulosides.

## Experimental

**High-Melting Form of Tetratosylsedoheptulosan (2,7-Anhydro-1,3,4,5-tetra-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulose).**—Haskins, Hann, and Hudson[4] reported that their tetratosylsedoheptulosan crystallized from acetone–ethyl ether in clusters of fine needles that melted at 96–97° and showed $[\alpha]^{20}D$ −73.0° (*c* 0.84, chloroform). When we prepared the same compound and recrystallized it from 95% ethyl alcohol or from aqueous acetone it separated as prisms that melted at 146–148°; from chloroform–pentane it separated as rosettes of tiny crystals with the same melting point. The rotation, $[\alpha]^{20}D$, was −72.3° (*c* 1, chloroform). A sample of the original compound prepared by Haskins, Hann, and Hudson was converted into the higher-melting form by recrystallization from ethyl alcohol. The higher-melting form, upon recrystallization from acetone–ethyl ether, yielded silky needles melting at 95–120°. A mixture of the higher- and lower-melting forms showed only the higher melting point of 146–148°.

*Anal.* Calcd. for $C_{35}H_{36}O_{14}S_4$: C, 51.97; H, 4.49; S, 15.85. Found: C, 52.02; H, 4.50; S, 15.85.

**2,7-Anhydro-4,5-*O*-isopropylidene-1,3-di-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulose.**—To a solution of 2.7 g. of 4,5-*O*-isopropylidenesedoheptulosan[4] in 35 ml. of dry pyridine was added 3 g. (1.35 mole equiv.) of *p*-toluenesulfonyl chloride. After 3 days at room temperature the mixture was poured onto crushed ice and the mixture was left in a refrigerator for 3 days. The aqueous pyridine solution was decanted from the deposited gum and the latter was washed with cold water. The gum crystallized readily from 95% ethyl alcohol and after two recrystallizations from the same solvent the 1 g. of plate-like crystals of the ditosylate melted at 131–132° and showed $[\alpha]^{20}D$ −79.0° (*c* 1, chloroform).

*Anal.* Calcd. for $C_{24}H_{28}O_{10}S_2$: C, 53.32; H, 5.22; S, 11.86. Found: C, 53.12; H, 5.54; S, 11.98.

**2,7-Anhydro-4,5-*O*-isopropylidene-1-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulose.**—The decantate and aqueous washings from the gum described above were combined and extracted with chloroform, and the extract was washed, dried, and concentrated in the usual manner. The sirupy product, in aqueous ethyl alcohol, crystallized after 2 weeks in a refrigerator. This monotosylate (1.5 g.) was recrystallized from chloroform–pentane from which it separated as clusters of rectangular prisms of m.p. 102–104° and $[\alpha]^{20}D$ −78.1° (*c* 1.3, chloroform).

*Anal.* Calcd. for $C_{17}H_{22}O_8S$: C, 52.84; H, 5.74; S, 8.30. Found: C, 52.77; H, 5.82; S, 8.02.

**Sedoheptulosan Triacetate (2,7-Anhydro-β-D-*altro*-heptulopyranose 1,3,5-Triacetate).**—The acetylation of 40 g. of sedoheptulosan hydrate with acetic anhydride and pyridine in the usual manner[1] yielded the sirupy tetraacetate. In one instance, however, dissolution of the sirup in ethanol resulted in the deposition of 2.5 g. of needles melting about 85–95° and apparently solvated. The anhydrous form of sedoheptulosan triacetate was obtained as prismatic needles by recrystallization from methanol: m.p. 119–120° and $[\alpha]^{20}D$ −155° (*c* 1, chloroform). No triacetate was ever isolated when the acetic anhydride–sodium acetate method of acetylation[13] was used.

*Anal.* Calcd. for $C_{13}H_{18}O_9$: C, 49.06; H, 5.70; $CH_3CO$, 40.6. Found: C, 49.03; H, 5.95; $CH_3CO$, 40.2.

**N.m.r. Data.**—The n.m.r. spectra were recorded on a Varian Model A-60 spectrometer; tetramethylsilane was used as the internal reference. We are indebted to Dr. John D. Stevens of this laboratory for the following interpretation.

Chapman and King[14] have shown that primary, secondary, and tertiary alcohols may be differentiated by examining the n.m.r. spectra using methyl sulfoxide as solvent, the hydroxyl hydrogens giving rise to a triplet, doublet, and singlet, respectively. The n.m.r. spectrum of **isopropylidenesedoheptulosan**[4] in methyl sulfoxide showed a doublet (7 c.p.s.) at τ 4.9 and a triplet (6.5 c.p.s.) at 5.33 overlying a broad 1-proton multiplet at 5.25. The addition of deuterium oxide to the solution caused the disappearance of the doublet and triplet at τ 4.9 and 5.33, respectively. It follows that the isopropylidenesedoheptulosan contains a primary and a secondary hydroxyl group. The position of the latter was established by examining the n.m.r. spectrum of isopropylidenesedoheptulosan dibenzoate[15] in deuteriochloroform. The spectrum showed a well-defined doublet at τ 4.43. The chemical shift, spacing (5 c.p.s.), and multiplicity of this signal showed that it must be due to a hydrogen on a secondary carbon bearing a benzoyloxy group (sedoheptulosan tetrabenzoate[4] in deuteriochloroform showed a 3-proton multiplet at τ 3.8–4.3, obviously due to secondary hydrogens on C-3, C-4, and C-5, the protons on C-1, C-6, and C-7 all appearing at higher field) and that the hydrogen must be coupled with only one neighboring hydrogen. Hence the secondary hydroxyl group in isopropylidenesedoheptulosan must be on C-3 and the compound may thus be formulated as 2,7-anhydro-4,5-*O*-isopropylidene-β-D-*altro*-heptulose.

The n.m.r. spectrum of the **monotosyl derivative of isopropylidenesedoheptulosan** in methyl sulfoxide showed a doublet (7 c.p.s.) at τ 4.50 that disappeared when deuterium oxide was added to the solution. The free hydroxyl group must therefore be secondary and the compound is 2,7-anhydro-4,5-*O*-isopropylidene-1-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulose.

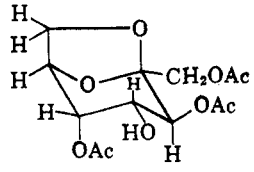
**Sedoheptulosan triacetate** (VI) was *O*-deuterated by adding deuterium oxide to an acetone solution of VI and evaporating the solution. The n.m.r. spectrum of the compound in a 1:2 mixture of acetone and benzene (at 66°, to overcome the low solubility of the compound in this mixture) showed, as the lowest-field signals, two 1-proton multiplets at τ 4.69 and 4.92; the former was a well-resolved doublet (spacing 9.0 c.p.s.) and the latter was an almost symmetrical quartet (spacings 2.3 and

(13) N. K. Richtmyer, *Methods Carbohydrate Chem.*, **1**, 169 (1962).

(14) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

(15) This compound was obtained in sirupy form by benzoylation of isopropylidenesedoheptulosan with benzoyl chloride and pyridine in the usual manner.

4.8 c.p.s.). At higher field ($\tau$ 5.97) another quartet (spacings 9.0 and 4.8 c.p.s.) could easily be identified. Of the other signals in the spectrum, four sharp peaks could be identified as the quartet of an AB pair ($J_{AB}$ = 12.0 c.p.s.; $\delta_{AB}$ = 0.67 p.p.m., centered at $\tau$ 5.70). As there are only two hydrogens giving rise to low-field signals, it follows that the free hydroxyl group in VI must be secondary. Further, the doublet at $\tau$ 4.69 could arise only from the proton on C-3 (the protons on C-3 and C-4 are *trans*-diaxially disposed[16]) and, as this proton is not coupled with the proton giving rise to the multiplet at $\tau$ 4.92, it follows that the free hydroxyl group must be on C-4. This assignment is verified by the splittings of the quartet at $\tau$ 5.97 which must be assigned to the proton on C-4. Therefore, the multiplet at $\tau$ 4.92 arises from the proton on C-5, the splitting pattern being consistent with a hydrogen so disposed.[16] Compound VI is, consequently, 1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-*altro*-heptulopyranose. The AB quartet at $\tau$ 4.69 is assigned to the geminal hydrogens on C-1.




VI

**Phenyl α-Sedoheptuloside Pentaacetate (Phenyl α-D-*altro*-Heptulopyranoside Pentaacetate).**—A mixture of 4.0 g. of sedoheptulose hexaacetate,[1] 8 g. of phenol, 2 g. of fused zinc chloride, 7.2 ml. of acetic acid, and 0.8 ml. of acetic anhydride was warmed until homogeneous and then heated *in vacuo* (water pump) for 2 hr. at 75–80°. The residue was dissolved in 125 ml. of chloroform and the extract was washed with water, twice with 3% aqueous sodium hydroxide, and with water. The washed extract was dried with sodium sulfate, filtered through decolorizing carbon, and concentrated in a current of air. The crystalline residue was filtered and washed with pentane to yield 3.6 g. (84%). After two recrystallizations from aqueous acetone the clusters of prismatic needles melted at 148–150° and showed $[\alpha]^{20}D$ +60.7° (*c* 1, chloroform).

*Anal.* Calcd. for $C_{23}H_{28}O_{12}$: C, 55.64; H, 5.69; $CH_3CO$, 43.4. Found: C, 55.79; H, 5.87; $CH_3CO$, 43.7.

**Phenyl β-Sedoheptuloside Pentaacetate (Phenyl β-D-*altro*-Heptulopyranoside Pentaacetate).**—From the mother liquors of five condensations each of 4 g. of sedoheptulose hexaacetate with phenol as described above (larger runs or the use of *p*-toluenesulfonic acid as catalyst resulted in lower yields) was obtained a total of 1.6 g. of a mixture of the anomeric glycoside acetates. By a combination of fractional crystallization from chloroform–pentane and mechanical separation 0.45 g. of the β-anomer was obtained. It formed clusters of flat, hexagonal prisms, melted at 129–131°, and showed $[\alpha]^{20}D$ −94.6° (*c* 0.9, chloroform).

*Anal.* Calcd. for $C_{23}H_{28}O_{12}$: C, 55.64; H, 5.69; $CH_3CO$, 43.4. Found: C, 55.34; H, 5.61; $CH_3CO$, 43.7.

**Phenyl α-Sedoheptuloside (Phenyl α-D-*altro*-Heptulopyranoside, I).**—To an ice-cold solution of 5 g. of phenyl α-sedoheptuloside pentaacetate in 100 ml. of methanol was added 2 ml. of 1.5 *N* sodium methoxide in methanol and the mixture was kept in a refrigerator at 5° for 48 hr. At the end of that time the solution was stirred with the weakly acidic Amberlite IRC-50 ion-exchange resin for 0.5 hr. to remove sodium ions, treated with decolorizing carbon to remove a slight yellow color, filtered, and concentrated *in vacuo* to a sirup that crystallized readily upon the addition of a small amount of ethyl alcohol. Most of the solvent was allowed to evaporate overnight and the product (2.5 g., 87%) was recovered by filtration and washing with pentane. The phenyl α-sedoheptuloside was recrystallized twice from ethyl alcohol–pentane from which it separated as prisms with m.p. 132–133° and $[\alpha]^{20}D$ +121° (*c*, 0.8 water). When oxidized with sodium metaperiodate, phenyl α-sedoheptuloside consumed 1.98 and 2.08 moles of oxidant and liberated 0.71 and 0.82 mole of formic acid/mole of compound at the end of 24 and 45 hr., respectively. The final rotation, calculated as the dialdehyde, was $[\alpha]^{20}D$ +131°. For comparison, the corresponding values were determined for phenyl α-D-*manno*-heptulopyranoside[9]: these were 1.82 and 2.01 moles of oxidant, 0.69 and 0.85 mole of acid, and $[\alpha]^{20}D$ +132°. For phenyl α-D-*gluco*-heptulopyranoside[8] the values were 1.79 and 1.87 moles of oxidant and 0.51 and 0.68 mole of acid at the end of 48 and 72 hr., respectively, with $[\alpha]^{20}D$ +141°.

*Anal.* Calcd. for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.35; H, 6.36.

**Phenyl β-Sedoheptuloside (Phenyl β-D-*altro*-Heptulopyranoside).**—Deacetylation of 440 mg. of phenyl β-sedoheptuloside tetraacetate in the same manner as described above for the α-anomer yielded 197 mg. (78%) of phenyl β-sedoheptuloside. The compound was recrystallized successively from ethyl alcohol–pentane, isopropyl alcohol–pentane, and ethyl alcohol–pentane; the rosettes of small crystals melted at 141–144° and showed $[\alpha]^{20}D$ −145° (*c* 0.8, water). The oxidation of phenyl β-sedoheptuloside with sodium metaperiodate consumed 1.97 and 2.02 moles of oxidant and liberated 0.89 and 0.91 mole of formic acid/mole of compound at the end of 4.5 and 24 hr., respectively. The rotation $[\alpha]^{20}D$ −50.8°, calculated for the dialdehyde, was constant after 4.5 hr.

*Anal.* Calcd. for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.81; H, 6.45.

**Lability of the Phenyl Sedoheptulosides toward Strongly Acidic Ion-Exchange Resins.**—When phenyl α-sedoheptuloside pentaacetate was deacetylated with sodium methoxide at 5° and the sodium ions were removed with Amberlite IRC-50 as described above, a sample of the solution chromatographed in butyl alcohol–pyridine–water (6:4:3) and sprayed with orcinol–HCl showed only a single spot, namely, that corresponding to phenyl α-sedoheptuloside. When this solution was left in contact with the strongly acidic Dowex 50 resin for only 5 min., however, a chromatogram showed a second blue spot, corresponding to sedoheptulose. Portions of the solution were then left over freshly washed Dowex 50 and Amberlite IR-120 resins for 3 days. The observed rotations changed from strongly positive ($\alpha^{20}D$ +8.5°) to negative ($\alpha^{20}D$ −1.5°), and chromatograms showed that most of the phenyl α-sedoheptuloside had been converted into sedoheptulosan. In the first deacetylation of phenyl α-sedoheptuloside pentaacetate, in which Amberlite IR-120 ($H^+$) was used to remove sodium ions from the aqueous solution, the only crystalline material that could be isolated was sedoheptulosan.

**Methyl α-Sedoheptuloside (Methyl α-D-*altro*-Heptulopyranoside).**—A solution containing 20 g. of sedoheptulose hexaacetate in 150 ml. of 30–32% hydrogen bromide in glacial acetic acid was allowed to stand for 2 hr. at room temperature, then diluted with 500 ml. of dichloromethane, poured onto cracked ice, and shaken in a separatory funnel. The dichloromethane layer was separated, the aqueous layer was shaken with 150 ml. of dichloromethane, and the combined extracts were washed in succession with cold water, cold 5% aqueous sodium bicarbonate, and cold water. The dichloromethane solution was dried with sodium sulfate, filtered through decolorizing carbon, and concentrated *in vacuo* to a dark sirup weighing 18 g. A solution of this sirup in 60 ml. of acetone was added to a stirred suspension of 20 g. of silver carbonate in 120 ml. of acetone and 20 ml. of water and stirring was continued overnight. The mixture was filtered and the silver salts were extracted thoroughly with acetone. The solutions were combined and concentrated to a sirup that was dissolved in absolute ethyl alcohol and dried three times by codistillation with benzene *in vacuo*. The residual sirup weighed 14.2 g. Methylation of this sirup was effected by shaking its solution in 175 ml. of iodomethane with 15 g. of silver oxide and 15 g. of Drierite for 3 days at 5°. The solution was filtered through carbon and the solid residue was washed thoroughly with ethyl ether. Concentration of the combined solutions left 12.7 g. of sirup. Catalytic deacetylation with methanolic sodium methoxide for 3 days at 5° was incomplete but eventually, after separation into water-soluble and water-insoluble fractions and redeacetylation of the latter fraction, about 0.3 g. of the desired methyl α-sedoheptuloside was obtained. Several recrystallizations from absolute ethyl alcohol furnished clusters of small prisms with m.p. 156–157° and $[\alpha]^{20}D$ +104° (*c* 0.5, water).

When 15 mg. of methyl α-sedoheptuloside was oxidized with sodium metaperiodate, it consumed 1.94, 1.96, and 1.96 moles of oxidant and liberated 0.63, 0.66, and 0.74 mole of formic acid/mole of compound at the end of 24, 48, and 96 hr., respectively. In comparison, methyl α-D-*gluco*-heptulopyranoside[17] consumed 1.82, 1.93, and 2.04 moles of oxidant and liberated 0.51, 0.62,

(16) R. U. Lemieux, R. K. Kullnig, H. F. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(17) W. C. Austin, *ibid.*, **54**, 1925 (1932).

and 0.78 mole of acid after the same periods of time; methyl α-D-*manno*-heptulopyranoside[10] consumed 1.93, 1.97, and 2.02 moles of oxidant and liberated 0.58, 0.65, and 0.84 mole of acid at the end of 24, 48, and 120 hr., respectively. The final rotations, calculated as the dialdehyde, were $[\alpha]^{20}D$ +111, +101, and +105° for the methyl α-D-*altro*, *gluco*-, and *manno*-heptulopyranosides, respectively.

**Methyl α-Sedoheptuloside Pentaacetate (Methyl α-D-*altro*-Heptulopyranoside Pentaacetate).**—The action of acetic anhydride and pyridine on methyl α-sedoheptuloside gave an 81% yield of the pentaacetate. It was recrystallized twice from chloroform–pentane as clusters of rods, m.p. 78–79° and $[\alpha]^{20}D$ +75.3° (*c* 0.7, chloroform).

*Anal.* Calcd. for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03; $CH_3CO$, 49.54; $OCH_3$, 7.14. Found: C, 49.98; H, 6.23; $CH_3CO$, 49.38; $OCH_3$, 6.94.

**Lability of the Phenyl Sedoheptulosides toward Methanolic Sodium and Barium Methoxides.**—When phenyl α-sedoheptuloside pentaacetate was treated with methanolic sodium methoxide for 48 hr. at 5°, as described above, only deacetylation occurred as was shown by paper chromatography and by isolation of the phenyl glycoside in 87% yield. When deacetylation was carried out similarly at 20°, paper chromatography yielded spots corresponding to methyl α-sedoheptuloside as well as phenyl α-sedoheptuloside. Deacetylation of 4 g. of phenyl α-sedoheptuloside pentaacetate in 350 ml. of methanol at 20° for 48 hr. with methanolic barium methoxide, followed by neutralization with carbon dioxide, removal of the methanol in a current of air, extraction of the residue with boiling acetone, and evaporation of the solvent, left 2.5 g. of sirup. This sirup was extracted with warm ethyl ether; the residual sirup was dissolved in absolute ethyl alcohol; and the solution was diluted with pentane and inoculated with phenyl α-sedoheptuloside to yield, slowly, 0.7 g. of that product in 2 crops. From the mother liquor was obtained 0.1 g. of a higher-melting compound that was recrystallized thrice from ethyl alcohol; the clusters of prisms melted at 155–157° and showed $[\alpha]^{20}D$ +108° (*c* 1, water). The substance was identified as methyl α-sedoheptuloside through analysis, mixture melting point, and comparison of its infrared spectrum with that of the methyl α-sedoheptuloside described earlier in this paper.

*Anal.* Calcd. for $C_8H_{16}O_7$: C, 42.85; H, 7.19. Found: C, 42.83; H, 7.14.

At 65°, the deacetylation of phenyl α-sedoheptuloside pentaacetate with methanolic sodium methoxide for 6 hr. yielded, according to paper chromatography, only methyl α-sedoheptuloside, and that substance could be isolated in crystalline form after the reaction. The unacetylated phenyl α-sedoheptuloside, after 2 hr. under the same conditions, appeared to have been converted practically completely into the methyl glycoside. Neither sedoheptulosan nor α-sedoheptulose hexaacetate furnished any methyl α-sedoheptuloside; the first compound appeared to be completely stable and the second compound to show no orcinol-positive material left after being heated with methanolic sodium methoxide. A 43-mg. sample of the phenyl β-sedoheptuloside (chromatographically free of the α-anomer), when heated similarly, led to the isolation of 5 mg. of crystalline methyl α-sedoheptuloside.

**Behavior of Some Other Phenyl Heptulosides and Phenyl Hexosides in Methanolic Sodium Methoxide.**—Phenyl α-D-*gluco*-heptulopyranoside pentaacetate[5] and phenyl α-D-*manno*-heptulopyranoside pentaacetate[9] showed no reaction other than deacetylation when they were treated with methanolic sodium methoxide at 5 or at 20° for 48 hr. and the solutions were examined by paper chromatography. The *gluco* compound was not changed further by boiling sodium methoxide in 48 hr. but the *manno* compound began to show a slight reaction after 14 hr. Accordingly, 0.2 g. of phenyl α-D-*manno*-heptuloside pentaaacetate was refluxed with 0.3 ml. of 1.3 *N* methanolic sodium methoxide in 10 ml. of methanol. Aliquots (0.5 ml.) were removed from time to time for chromatographic examination. Finally, after 168 hr., the reaction had reached a point where a paper chromatogram showed the spots corresponding to phenyl and methyl α-D-*manno*-heptuloside to be of about equal intensity. The remaining solution was decationized with Amberlite IRC-50 resin, concentrated, and chromatographed on four large sheets of Whatman No. 1 paper overnight in butyl alcohol–pyridine–water (6:4:3) The sections containing the slower-moving material were cut out and extracted with water. Concentration yielded 30 mg. of sirup that did not crystallize. It was acetylated by dissolving in 1 ml. of dry pyridine and 0.3 ml. of acetic anhydride. Two days later 5 g. of ice was added and, after the ice had melted, the mixture was freeze dried. The residue was extracted with ethyl ether, the extract was concentrated to a sirup, and the sirup was inoculated with authentic methyl α-D-*manno*-heptulopyranoside pentaacetate.[10] The yield of crystalline product was 52 mg.; after recrystallization from ethyl ether–pentane it melted at 59–62° and the melting point was not depressed when the product was mixed with known methyl α-D-*manno*-heptuloside pentaacetate (m.p. 64°).

For comparison with the phenyl heptulosides, four phenyl hexopyranosides were refluxed in methanolic sodium methoxide. The results given below are based solely on paper chromatographic evidence. Phenyl β-D-alloside[3] was converted almost completely within 53 hr. into 1,6-anhydro-β-D-allopyranose.[18] Phenyl β-D-galactoside reacted in 96 hr. to give a small amount of 1,6-anhydro-β-D-galactopyranose. Phenyl α-D-alloside[3] was not attacked in 48 hr. and phenyl α-D-mannoside was not in 120 hr. The latter, however, when heated with sodium methoxide in methyl sulfoxide for 60 hr. at 70°, gave as the main product a compound with the mobility of methyl α-D-mannopyranoside and no evidence for the presence of any 1,6-anhydro-β-D-mannopyranose. It has been reported earlier that phenyl β-D-glucoside was unchanged by boiling in methanolic sodium methoxide for 5 hr.,[19] whereas 2,4,6-tribromophenyl β-D-glucoside dissolved slowly but completely in that reagent at room temperature in the course of 2 or 3 days, and 21% of methyl β-D-glucopyranoside and 75% of 1,6-anhydro-β-D-glucopyranose could be isolated from the solution.[20]

**Behavior of the Phenyl α- and β-Sedoheptulosides and of the Phenyl α-D-*gluco*- and *manno*-Heptulopyranosides in 0.5 *N* Aqueous Potassium Hydroxide at 20°.**—When 0.3 g. of phenyl α-sedoheptuloside was dissolved in 10 ml. of 0.5 *N* potassium hydroxide the rotation dropped from $\alpha^{20}D$ +2.0° (3 min.) to +0.2° in 3 hr. and then rose slightly for several days thereafter. Aliquots were removed at frequent intervals, neutralized at once with Amberlite IRC-50 resin, and examined by paper chromatography. The orcinol–hydrochloric acid spray showed that the glycoside had practically disappeared by the end of 3 hr., that sedoheptulose was formed as the glycoside disappeared, and that there was no evidence for the presence of sedoheptulosan or D-*allo*-heptulose (the epimer of sedoheptulose). The odor of phenol was detected after 45 min. In the similar reaction of 20 mg. of phenyl β-sedoheptuloside the observed rotation changed from $\alpha^{20}D$ −0.3° (4 min.) to −0.2° (7 hr.) to −0.1° (24 hr.) to ±0° (48 hr.). Paper chromatograms of the 24-hr. sample showed that sedoheptulose was formed at the expense of the phenyl β-sedoheptuloside and that the formation of any sedoheptulosan was very doubtful.

Phenyl α-D-*gluco*-heptuloside appeared to be unaffected by 0.5 *N* potassium hydroxide in 4 days, for the rotation did not change and a paper chromatogram showed only the starting material. The behavior of phenyl α-D-*manno*-heptuloside (0.25 g.) in 10 ml. of 0.5 *N* potassium hydroxide at 20° was followed polarimetrically and paper chromatographically. The observed rotation dropped from $\alpha^{20}D$ +2.2° to +1.9° in 24 hr., to +1.7° in 48 hr., and then more slowly to about 0° in the dark solution after 40 days. As the amount of phenyl α-D-*manno*-heptuloside decreased, D-*gluco*-heptulose appeared to be formed, but no D-*manno*-heptulose (these heptuloses are separable on Whatman No. 1 paper by chromatography for 90 hr., in a 95:5 acetone–water mixture), and 2,7-anhydro-β-D-*manno*-heptuloypyranose also seemed to be present. In related experiments, D-*manno*-heptulose in 0.5 *N* potassium hydroxide after 27 hr. showed, on paper chromatograms, the presence of D-*manno*- and D-*gluco*-heptuloses in about equal amounts; after 4 days only the D-*gluco* epimer could be detected. However, D-*gluco*-heptulose under the same conditions showed no indication of epimerization to D-*manno*-heptulose. Degradation in all cases resulted in eventual disappearance of the free heptuloses.

Confirmation of the conclusions reached from the small-scale phenyl α-D-*manno*-heptuloside reaction just described was obtained by dissolving 11.5 g. of the glycoside in 600 ml. of 1 *N*

(18) J. W. Pratt and N. K. Richtmyer, *J. Am. Chem. Soc.*, **77**, 1906 (1955).

(19) E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *J. Org. Chem.*, **10**, 194 (1945).

(20) L. H. Koehler and C. S. Hudson, *J. Am. Chem. Soc.*, **72**, 981 (1950).

potassium hydroxide and letting the mixture stand at 20° for 9 days. The dark solution was neutralized with carbon dioxide, treated with decolorizing carbon, extracted with chloroform, deionized by passage through Amberlite IR-120 and Duolite A-4 ion-exchange columns, and the neutral solution concentrated to a sirup that weighed 4.3 g. This sirup was fractionated on a cellulose column with benzene–ethyl alcohol–water mixtures as eluent. Two orcinol-positive fractions were obtained: the first (1.1 g.) yielded 0.55 g. of crystalline 2,7-anhydro-β-D-*manno*-heptulopyranose, the second (1.4 g.) 0.65 g. of D-*gluco*-heptulose.

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# Nucleosides. XXIII. 2′,5′- and 3′,5′-Epoxides of Pentofuranosyluracils[1-3]

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Treatment of 1-(5′-*O*-mesyl-2′,3′-epoxy-β-D-lyxosyl)uracil (Ib) with sodium benzylate effects epoxide opening with the formation of 1-(2′,5′-epoxy-3′-*O*-benzyl-β-D-arabinosyl)uracil (X). Hydrogenation of X using palladium–charcoal catalyst gave 1-(2′,5′-epoxy-β-D-arabinofuranosyl)uracil (II). As a proof of structure, epoxide II was synthesized from 1-(5′-*O*-mesyl-β-D-arabinofuranosyl)uracil (VIIb). Both the arabino nucleoside VIIb and 1-(5′-*O*-mesyl-β-D-xylofuranosyl)uracil (VIIIb) were synthesized by opening the epoxide ring of the 5′-*O*-mesyl 2′,3′-epoxide Ib with aqueous sulfuric acid. As proof of structure, arabino nucleoside VIIb was converted to the known tri-*O*-mesylarabinosyluracil. The 5′-mesylated nucleosides VIIb and VIIIb reacted intramolecularly in aqueous alkali, and yielded as sole products 1-(2′,5′-epoxy-β-D-arabinofuranosyl)uracil (II) and 1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil (III), respectively. Hydrolysis of 5′-*O*-mesyl- and 5′-iodo-arabinosyluracils (VIIb and XIX) under slightly acid conditions gave 2,2′-anhydroarabinosyluracil (XXI), together with the 2′,5′-epoxide II and 1-β-D-arabinofuranosyluracil (VIIa). The novel conversion of VIIb and XIX to the 2,2′-anhydro nucleoside XXI is postulated as occurring *via* a 2,5′-anhydroarabinosyluracil intermediate. Hydrolysis of 5′-*O*-mesylxylosyluracil (VIIIb) under the same conditions as VIIb gave 2,3′-anhydroxylosyluracil (XXII), together with the 3′,5′-epoxide III and 1-β-D-xylofuranosyluracil (VIIIa). It is postulated that the anhydro nucleoside XXII arises by attack of the 3′-hydroxyl group at C-2 of a 2,5′-anhydroxylosyluracil intermediate.

Recent reports have described the syntheses of a wide variety of uracil nucleosides from trimesyloxyuridine.[4-8] Among these compounds 1-(2′,3′-epoxy-β-D-lyxofuranosyl)uracil and its 5′-mesyloxy derivative (I, Figure 1) have been shown to be useful intermediates in the preparation of other 1-β-D-aldopentofuranosyluracil analogs of potential biological interest.[6] Of the six possible epoxypentofuranosyluracils (I–VI, Figure 1) only one, the 2′,3′-epoxide I of the *lyxo* configuration, has been reported.[9] The present paper describes the syntheses and properties of 1-(2′,5′-epoxy-β-D-arabinofuranosyl)uracil (II) and 1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil (III) from the 2′,3′-epoxide Ib. It was anticipated that these epoxides would be valuable intermediates in the syntheses of biologically active pyrimidine nucleosides. Epoxides IV and V will be reported in the next paper.[10]

Epoxypentofuranosides in which the epoxide ring is a propylene or butylene oxide type have been reported. These dicyclic furanosides were synthesized by the intramolecular displacement of a 5-sulfonyloxy group by a 2- or 3-alkoxide ion, where the sulfonyloxymethyl group and the attacking alkoxide ion were in *cis* relationship. The known examples of these are methyl-(ethyl) 2,5-epoxy-α-L-arabinofuranoside prepared by Cifonelli and associates,[11] and 1-[2′-deoxy-3′,5′-epoxy-β-D-lyxo(xylo)syl]thymine synthesized by Horwitz and co-workers.[12] Levene and Raymond[13] have described the conversion of 1,2-*O*-isopropylidene-5-*O*-tosyl-D-xylose by sodium methoxide to 1,2-*O*-isopropylidene-3,5-epoxy-D-xylose.

The synthesis of the 2′,5′- and 3′,5′-epoxy nucleosides (II and III) required the availability of 1-(5′-*O*-Ms-β-D-arabinofuranosyl)uracil (VIIb) and 1-(5′-*O*-Ms-β-D-xylofuranosyl)uracil (VIIIb), respectively (Figure 2). The obvious starting material for the arabino nucleoside VIIb was the 5′-*O*-mesyl 2′,3′-epoxy derivative Ib. The opening of the epoxide linkage in Ib with various nucleophilic reagents under basic or acidic conditions was expected to yield products with predominently the *arabino* configuration *via* nucleophilic attack at C-3′.[6,14] A second reaction, the replacement of the 5′-mesyloxy group of Ib by

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant CA 03190-08).

(2) A preliminary report has appeared: see I. L. Doerr, J. F. Codington, and J. J. Fox, Abstracts, 145th Meeting of the American Chemical Society, New York, N. Y., Sept. 1963, p. 19D.

(3) In accordance with the suggestion (see ref. 6), the term "epoxy" is used to refer to an ether linkage in the sugar moiety. The term "anhydro" (as "anhydro nucleoside") refers to an oxygen bridge between the C-2 of the pyrimidine and C-2′, C-3′, or C-5′ of the sugar moiety.

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